Universität Zürich
Zentrum für Zahnmedizin
Klinik für Mund- Kiefer- und Gesichtschirurgie
Direktor: Prof. Dr. med. Dr. med. dent. K. W. Grätz

Arbeit unter Leitung von Dr. med. C. Jacobsen

Bisphosphonate Related Osteonecrosis of The Jaws: Cases Reviews

INAUGURAL-DISSERTATION
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vorgelegt von
Giselle Llerena Garcia de Richterich
aus Lima-Peru

Genehmigt auf Antrag von Prof. Dr. med. Dr. med. dent. K. W. Grätz
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I ABSTRACT

Purpose:
Bisphosphonate related osteonecrosis of the jaw (BRONJ) is a seide effect of long-term bisphosphonate therapy in cancer patients. The following document presents a cases review at the oral and maxillofacial department from the University Hospital in Zürich, Switzerland.

Materials and Methods:
This review evaluated 56 medical records of patients with Osteonecrosis of the Jaw and Bisphosphonate history. One record had to be excluded due to the fact that the patient had radiation therapy in the area of clinical symptoms. The patients who fulfilled the entry criteria underwent retrospective analysis. Available data on demographics, medical history, type and duration of BP use, possible triggering event, clinical manifestations, mode of therapy and outcome were recorded on different tables on an Excel programm.

Results:
BRONJ was associated with intravenosu bisphosphonates in 90.7% of the cases and with oral bisphosphonates in 9.2%. Of the patients, 66.6% received zolendronic IV while 80% were taking fosamax orally. The mean duration from the first use of the drug to the recognition of sign or symptoms of ONJ was 39 months.The first and most frequent first symptom was pain. The clinical manifestation included halitosis, hypesthesia, pus exsudates, swelling, non-healing wounds and exposed bone. Before the occurrence of BRONJ, 71.7% of the patients have had one or more tooth extracted. Surgical treatments were done in 57.4% and no surgical treatments which involved only antibiotics were done in 42.5%. Of the patient 38.2% had a complete remission after therapy.

Conclusion:
Solutions for a better outcome after therapy for BRONJ remain elusive.

II INTRODUCTION

Osteonecrosis, also referred to avascular necrosis of bone, aseptic necrosis, ischemic necrosis, or oteochondritis dissecans, is the death of a segment of bone caused by an imparied blood supply. This disorder can be caused by an injury or can occur spontaneously, but is not a specific disease but rather a condition in which there is death of a localized area of bone.[1]

There are two principal groups of patients that are affected with this disorder. The first group suffers from osteoradionecrosis[2,3,4]. Its most severe form, called infected osteoradionecrosis (IORN), frequently presents as a chronic disease that is highly resistant against therapeutic interventions. The clinical symptoms include pain, chronic fistulation, exposed bone, and even extended bone destruction and pathological bone fracture[3,5,6].

Recently, a second type of osteonecrosis has been observed to involve the jaws during long term of antiresorptive bone treatment. This type was first report by Marx in 2003[7]. Since then, Roelofs et al describes that there have been several clinical reports have emerged which report the incidence of osteonecrosis of the jaws in non radiated patients but who are receiving bisphosphonate therapy[8].

According to the American Association of Oral and Maxillofacial Surgeons (aaoms), bisphosphonate-related osteonecrosis of the jaw (BRONJ) is defined by three main characteristics: previous or current bisphosphonate therapy, exposed necrotic bone in the maxillofacial region that has been persisted for more than 8 weeks, and no radiation of the jaws[9].
If these three conditions are present, the diagnosis can be confirmed clinically. It is important to exclude local malignancy, trauma, periodontal disease, and lingual mandibular sequestration and ulceration[10].

Bamias et all explained on his article that the incidence among cancer patients receiving high-dose intravenous bisphophonates shows osteonecrosis of the jaw as dependent on dose and duration of therapy, and has an estimated incidence of 1% to 12%[9,11].

Among patients treated for 4–12 months, the incidence increases with the time of exposure, from 1.5% to 7.7% compare to those in treatment for 37–48 months[11].

In a clinical report done in Thailand, BRONJ typical clinical presentation includes: pain, soft-tissue swelling and infection, loosening of teeth, drainage and exposed bone[12]. These described symptoms may occur spontaneously, or more commonly, at the site of previous tooth extraction or other local invasive procedures. Patients may also present with feeling of dysesthesias, heaviness and numbness of the jaw. However, BRONJ may remain asymptomatic not only for weeks but also months, and will only become evident after finding exposed bone in the jaw[12].

Bisphoshonates represent a family of compounds of the general structure H2PO3-CR_1R_2-H2PO3. Woo & Gellstein descreibes the primary mechanism of action of bisphosphonates as the inhibition of osteoclastic resorption of the bone[8,13]. They can be grouped into several pharmacologic classes. The most potent class consists of nitrogen-containing bisphosphonates such as alendronate, pamidronate, and zoledronate[14].

The reduction of skeletal-related events such as fractures is one of the positive effects of the bisphosphonates. They also prevent hypercalcaecemic episodes, reduce pain and increas patients'qualitity of life[15].

Bisphosphonates are used in the treatment of metabolic bone diseases such as osteoporosis and Paget's disease of bone and also at much higher doses and potency in cases where cancers are involve skeletal sites, most commonly when treating multiple myeloma. In each of these cases the purpose of bisphosphonate treatment is to prevent bone loss, reduce fracture risk, and a direct anticancer effect.

On the other hand, adverse effects when using bisphosphonate have been observed. Such as: acute-phase reactions, adverse side-effects affecting the upper aerodigestive tract and some others affecting the kidneys[15].

III OSTEONECROSIS OF THE JAWS

III.1 Chemical Osteonecrosis

Necrosis of the jaws can occur as a result of contact with caustic chemicals and protoplasmic poisons. The condition may arise in industrial workers exposed to noxious substances. Alternatively, the chemicals may be administered either therapeutically or inadvertently, or as a result of a clinical accident. The extent of the bone damage varies according to the quantity and nature of the chemical responsible, and the condition often is complicated further by a superimposed pyogenic infection[16].

III.1.1 Phosphorus necrosis

The most documented of the chemicals agents causing necrosis of the jaws is phosphorus. There is no consensus as to the exact etiology of the condition, but the fumes that emanate are phosphorous anhydride (P_2O_3) and phosphoric anhydride (P_2O_5). These, in conjunction with superadded bacterial infection, are considered to be responsible[17].

The lesion may occur following tooth extraction or alveolar abscess even many months after exposure to the fumes. Kennon and Hallam[17] state thath phosphorus necrosis may occur up to two years after a worker has left employment in which phosphorus fumes were present.

The jaw is particulary susceptible to necrosis due to the fact that it is subject to pyogenic infection arising from the teeth or tooth socket and the bone may be infected through an abrasion in the mucosa or by ulceration of the gingival.

Patients with phosphorus necrosis look and feel ill, but the temperature is only slightly elevated[16].

III.2 Necrosis following therapy with

III.2.1 Mercury

The disease is limited to the alveolar portion of the upper and lower jaw. The sequestra extruded consist of portions of alveolus with attached teeth. Bone changes are secondary to a mercurial stomatitis, the extension occurring from the necrotic gingival mucosa along the periodontal membrane of the standing teeth.

III.2.2 Arsenic Trioxide

Arsenic Trioxide was used to be employed to effect desvitalization of the dental pulp, but leakage via the tooth apex is likely to produce a localised necrosis of bone[16].

III.2.3 Radiation

Radiation of bone results in permanent damage to the osteocytes and microvasculature system. The altered bone becomes hypoxic, hypovascular, and hypocellular. It is the result of nonhealing, dead bone; infection is not necessarily present[18].

Although most instances arise secondary to local trauma, a minority appears spontaneous. The mandible is involved most frequently, although a few cases have involved the maxilla. Affected areas of bone reveal ill-defined areas of radiolucency that may develop zones of relative radiopacy as the dead bone separates from the residual vital areas. Intractable pain, cortical perforation, fistula formation, surface ulceraton, and pathologic fracture may be present[18].

The radiation dose is the main factor associated with bone necrosis, although the volume of bone irradiated and the proximity of the maximal dosing both exert an effect. The risk of bone necrosis increases in the presence of the

following: teeth, bone trauma, periodontal disease and concurrent chemotherapy[18].

III.2.4 Bisphosphonate

Bisphonate induced osteonecrosis of the jaw is refered to a condition characterized by exposure of bone in the mandible or maxilla persisting for more than 8 weeks in a patient who has taken or currently is taking a bisphosphonates and who has no history of radiation therapy to the jaws. However, while the exposed bone is indeed dead (osteonecrosis), bone death is actually a secondary result of bisphosphonates bone toxicity, or osteopetrosis[19].

Clinically, the disease presents as exposed alveolar bone, with or without pain, swelling and fistula formation and that occurs spontaneously or becomes evident following an invasive surgical procedure such as tooth removal, periodontal surgery, apicoectomy, or dental implant placement[19,20].

The disease manifests only in the jaws and to date has not been reported in other skeletal sites. It originates in the alveolar bone and may then extend to the basilar bone or ramus. Occasionally, early subclinical radiographic signs – including sclerosis of the lamina dura, loss of the lamina dura and/or widening of the periodontal ligament space particularly in association with molar teeth[19].

Greenberg M, Glick M, Ship J explained that the cumulative incidence is rising to be 10% after 3 years of drug use of intravenous bisphosphonates; with oral bisphosphonates, the risk is less, but still can produce BRONJ[20].

V. BISPHOSPHONATES

IV.1 Bisphosphonates concept

Bisphosphonates are pyrophosphate analogues, characterized by a P-C-P containing central structure rather than the P-O-P of pyrophosphate, and a variable side chain[8]. Coleman explained that the P-C-P backbone renders bisphosphonates resistant to the activity of phosphatase in order to promote their binding to the mineralised bone matrix[21].

An affinity for sites of active bone turnover is evident by their increased uptake in growth plates, bone grafts, and scans of normal maxillae and mandibles. Pyrophosphates are easily broken down via hydrolysis and eliminated. Because of their substion of carbon for oxygen in the backbone of the molecule, bisphosphonates are completely resistentant to hydrolytic breakdown, hence their accumulation in the bonematrix and extremely long half-life. In addition, substitution of nitrogen-containing side chains in the backbone carbon of bisphophonates increases potency[21].

To date, only nitrogen-containing bisphosphonates have been known to produce osteonecorsis of the jaws. They can be administerd either orally or intravenously[21].

IV.2 Modes of action

The fundamental biologic action of all bisphosphonates is to inhibit bone resorption and hence bone turnover and renewal, which of course reuses serum calcium levels as well.

The reason for this antiosteoclastic or anti-resorption effect is the inhibition and/or irreversible cell death of the osteoclast. Upon intravenous or oral administration, the bisphosphonate is bound to the mineral crystals on every bone surface. Repeated doses of bisphosphonate accumulate in the bone matrix.

During normal bone remodeling, osteoclast resorb the bone and ingest the bisphosphonate, which functions as an analogue of the isoprenoid diphosphate lipids are essential for farnesylation and geranylgeranylation of guanosine triphosphate (GTPase) enzymes, which prevent osteoclast apoptosis[22]. This biosynthetic pathway is also known as the mevalonate branch pathway.

Microscopically, the osteoclast is observed to lose its normal ruffled border at the Howship lacuna resorption site; retract from the bone surface, and die. Without bone resorption and the concomitant release of bone induction proteins such as bone morphogenetic protein (BMP) and isulinlike growth factors 1 and 2 (ILG_1 and ILG_2), old bone is not removed and new osteoid is not formed.

The old bone therefore survives far beyond its programmed lifespan. Since the osteocyte is not an inmortal cell, it eventually dies, leaving dead bone behind. The function of the osteocyte is to act as a mechanoreceptor to maintain the mineral matrix of existing bone. Therefore, if the osteocyte outlives the dictates of normal bone remodeling, it adds further mineral matrix to the bone. The mention hypermineralizaton is observed as being associated with bisphosphonate toxicity shown as sclerosis of the lamina dura, which is followed by a more generalized osteosclerosis in the alveolar bone.

IV.3 Pharmacocinetics

Oral bisphosphonates are absorbed in the small intestines, although poorly, only 1% to 10% is made available to bone. If the bisphosphonate is taken with meals, absorption is further reduced. The circulating half-life of oral and intravenous bisphosphonates ranges from a scant of 0.5 hours to a maximum of 2 hours. Attesting to its rapid uptake into bone matrix, where 30% to 70% of the intravenous or absorbed dose accumulates in bone. The remainder is excreted unchanged in the urine[19].

Repeated doses accumulate in bone matrix and can be removed only by osteoclast-mediated resorption as part of the bone turnover cycle. Bisphonates are toxic to

osteoclasts and prevent bone turnover, therefore, bisphophonate bone toxicity is both dose and time dependent[19].

In Coleman's report, it is stated that aproximately 50 – 75% of the injected dose (Intravenous bisphosphonates) binds avidly to mineral exposed bone, where it is internalised by the osteoclast during bone esorption and the remainder is excreted by the kidney[21].

IV.4 Clasifications according to the WHO Colaborating Centre for Drug Statistic Methodology

M **MUSCULO-SKELETAL SYSTEM**
M05 **DRUGS FOR TREATMENT OF BONE DISEASES**
M05B **DRUGS AFFECTING BONE STRUCTURE AND MINERALIZATION**
M05BA **Bisphosphonates**

ATC Code	Name	DDD	U	Adm.R
M05BA01	etidronic acid	0.4	g	O
		1.5	g	P
M05BA02	clodronic acid	1.6	g	O
		1.5	g	P
M05BA03	pamidronic acid	60	mg	P
M05BA04	alendronic acid	10	mg	O
M05BA05	tiludronic acid	0.4	g	O
M05BA06	ibandronic acid	6	mg	P
		5	mg	O
M05BA07	risedronic acid	5	mg	O
M05BA08	zoledronic acid	4	mg	P

IV.5 Bisphosphonates used in Switzerland[23]

ACLASTA

- ATC-Code: M05BA08
- Swissmedic: 57363
- Active Ingredient: Acidum Zoledronicum
- Company: Novartis Pharma Schweiz AG, Bern

BONEFOS

- ATC-Code: M05BA02
- Swissmedic 50957, 50958
- Active Ingredient: Dinatrii clodronas anhydricus
- Company Bayer (Schweiz) AG, 8045 Zürich.

PAMIDRONAT TEVA

- ATC-Code: M05BA03
- Swissmedic: 58855
- Active Ingredient: Dinatrii pamidronas anhydricus
- Company: Teva Pharma AG, 4147 Aesch

AREDIA

- ATC-Code: M05BA02
- Swissmedic: 52092
- Active Ingredient: Dinatrii pamidronas.
- Company: Novartis Pharma Schweiz AG, Bern

BONIVIA

- ATC-Code: M05BA06
- Swissmedic: 57526
- Active Ingredient: Acidum ibandronicum
- Company: Roche Pharma (Schweiz) AG, 4153 Reinach

ZOMETA

- ATC-Code: M05BA08
- Swissmedic: 56257
- Active Ingredient: Acidum Zoledronicum
- Company: Novartis Pharma Schweiz AG, Bern

BONDRONAT

- ATC-Code: M05BA06
- Swissmedic: 53626, 56360, 57424
- Active Ingredient: Acidum ibandronicum
- Company: Roche Pharma (Schweiz) AG, 4153 Reinach

There are many other bisphosphonates used in Switzerland which can be found at the Swiss Farmacological Compendium, those being described here had relevanz higher as 3%.[23]

IV.6 Bisphosphonates used in the United States of America (According to the US Food and Drugs Administration FDA)

DIDRONEL

- FDA Application No.: (NDA) 017831
- Active Ingredient: ETIDRONATE DISODIUM
- Company: PROCTER AND GAMBLE
- Original Approval Date: September 1, 1977

SKELID

- FDA Application No.: (NDA) 020707
- Active Ingredient: TILUDRONATE DISODIUM
- Company: SANOFI AVENTIS US
- Original Approval Date: March 7, 1997

FOSAMAX

- FDA Application No.: (NDA) 020560
- Active Ingredient: ALENDRONATE SODIUM
- Company: MERCK AND CO INC
- Original Approval Date: September 29, 1995

AREDIA

- FDA Application No.: (NDA) 020036
- Active Ingredient: PAMIDRONATE DISODIUM
- Company: NOVARTIS
- Original Approval Date: October 31, 1991

ACTONEL

- FDA Application No.: (NDA) 020835
- Active Ingredient: RISEDRONATE SODIUM
- Company: PROCTER AND GAMBLE
- Original Approval Date: March 27, 1998

BONIVA

- FDA Application No.: (NDA) 021455
- Active Ingredient: IBANDRONATE SODIUM
- Company: ROCHE
- Original Approval Date: May 16, 2003

ZOMETA

- FDA Application No.: (NDA) 021223
- Active Ingredient: ZOLEDRONIC ACID
- Company: NOVARTIS
- Original Approval Date: August 20, 2001

RECLAST

- FDA Application No.: (NDA) 022080
- Active Ingredient: ZOLEDRONIC ACID
- Company: NOVARTIS PHARMS
- Original Approval Date: August 17, 2007

IV.7 Medical Use:

Commonly used to treat patients with osteoporosis and neoplasias, especially in the case of lytic bone metastases (generated from breast and prostate cancer) and multiple myeloma, bisphosphonates reduce such skeletal complication as pain, pathologic fractures, limited mobility, malignant hypercalcemia, and spinal cord compression[24].

Franca Dore et all explaines that intravenous bisphosphonates are primarily used as an effective treatment and management of cancer-related conditions. These conditions include hypercalcemia of malignancy, skeletal-related events associated with bone metastases which present solid tumors including breast cancer, prostate cancer and lung cancer, and last but not least in the management of lytic lesions in the setting of multiple myeloma. The IV bisphosphonates are effective in preventing and reducing hypercalcemia, stabilizing bony pathology and preventing fractures in the context of skeletal involvement. While they have not been shown to improve cancer-specific survival, they have had a significant impact on the quality of life for patients with advanced cancer that involves the skeletal system[24].

Oral bisphosphonates are approved as a treatment for osteoporosis and are frequently used as a treatment for osteopenia as well. They are also used for a variety of less common conditions such as Paget's disease of bone, and osteogenesis imperfecta of childhood. In different clinical reports[25,26] the most prevalent and common indication reported is , however, osteoporosis. Osteoporosis may appear in the context of other diseases including inflammatory bowel disease or primary biliary cirrhosis, which are the result of medications, such as steroids (most commonly), or as a consequence of postmenopausal aging. Whatever the underlying etiology of the osteoporosis, bisphosphonates may play a role, perhaps in conjunction with calcium and vitamin D, in its management[27].

IV.8 Treatment Benefits

IV.8.1 Prevent skeletal morbidity and relief of bone pain

Bisphonates provide an additional treatment approach to radiotherapy, especially for patients with poorly localised bone pain or recurrence of bone pain in previosly irradiated sites.

Bisphonates have become the standard of care for the treatment and prevention of skeletal complications associated with bone metastase in patients wiht breast cancer and multiple myeloma[21].

IV.9 Treatment Complications

When cancer therapies are compared, bisphosphonate therapy ‘s frequency and severity of adverse events are generally mild and infrequent, thus, the benefits of treatment with any bisphosphonate, either taken orally or intravenously, almost always outweight the risks. According to Coleman, the side effect profile is mostly influenced by the administration route. Around 15-30% of patients with intravenous bisphosphonates will experience an acute phase reaction characterized by transient fever with muscle and joint aches; however, this usually only follows the first infusion and is largely irrelevant thereafter. Some data suggest that the incidence of the acute phase response is lesss common in immunocompromised advanced cancer patients than in healthy subjects or in those without metastases[21].

IV.9.1 Renal complications:

When patients are given high doses (above standard) or a rapid infusion with intravenous agents, renal abnormalities have been described. However, renal toxicity is unusual, usually predictable and reversible, when any bisphosphonate is given at the recommended dose and schedule. Serious

bisphosphonate-induced renal complications including renal failure are rare (less than 0.5%).

Because renal dysfunction is infrequent, none of the placebo-controlled trials with ibandronate or zolendronic acid showed any statistically significant differences between active therapy and placebo in creatinine levels with time. However, idiosyncratic renal abnormalities undoubtely do occur. A focal glomerulosclerosis asssociated with nephrotic syndrome is described when using pamidronate whereas when using zoledronic acid, renal abnormalities relate to tubular damage[21].

IV.9.2 Osteonecrosis of the jaw

In recent years, BRONJ has become one of the most discussed adverse events in advanced malignancy. Since the original reports of ONJ associated with the use of bisphosphonates were produced in 2003, over 1000 other cases have come to the attention of regulatory authorities around the world. The pathogenesis of BRONJ remaisn obscure and prospective research is requierd to determine it[21]

V. BISPHOSPHONATES RELATED OSTEONECROSIS OF THE JAWS

The AAOMS, in order to distinguish Bisphosphonates-related osteonecrosis of the jaws (BRONJ) from other delayed healing conditions, has adopted the following working definition of BRONJ:

When the following characteristics are present together, a patient may be considered to have BRONJ:

1. Current or previous treatment with a bisphosphonate;

2. Exposed, necrotic bone in the maxillofacial region that has persisted for more than eigh weeks

3. No history of radiation therapy to the jaws[27].

V.1 Risk factors

The following groups including: drug-related, local risk factors and demographic/systemic factors have been define in order to organise the possible risk factors for the development of BRONJ[27].

V.1.1 Drug-related risk factors

V.1.1.1 Particular bisphosphonate potency

Zoledronate is more potent than pamidronate, which is more potent than the oral bisphosphonates; therefore the IV route of administration results in a greater drug exposure than the oral route.

V.1.1.2 Duration of therapy

The longer duration appears to be associated with increased risk.

V.1.2 Local risk factors

V.1.2.1 Dentoalveolar surgery

Including, but not limited to:

1. Extractions
2. Dental implant placement
3. Periapical surgery
4. Periodontal surgery (involving bone injury)

Patients who while taking intravenous bisphosphonates are undergoing dentoalveolar surgery are at least seven times more likely to develop BRONJ than patients who are not having dentoalveolar surgical procedures.

V.1.2.2 Local anatomy

1. Mandible
    a. Lingual tori
    b. Mylohyoid ridge

2.Maxilla
    a. Palatal tori

It has been observed a 2:1 mandible-maxilla ratio representing that lesions are found more commonly in the mandible than the maxilla, specially in areas with thin mucosa overlying bony prominences such as tori, bony exostoses and the mylohyoid ridge.

V.1.2.3Concomitant oral disease

The risk for developing BRONJ are seven times more in patients with a history of inflammatory dental disease, such as periodontal and/or dental abscesses [27].

V.1.3 Demographic and systemic factors

- Age

According to the AAOMS with each decade that passes, there is a 9% increased risk for BRONJ in multiple myeloma patients treated with IV bisphosphonates.

- Race

Caucasian

- Cancer diagnosis

Patients with multiple myeloma have a greater risk than patients with breast cancer; and those last ones with breast cancer have a greater risk than those with other cancers.

- Other diagnosis

Osteopenia/osteoporosis diagnosis concurrent with cancer diagnosis

V.1.4 Other risk factors

The following are thought to be risk factors of BRONJ according to the AAOMS,

1. Corticosteroid therapy
2. Diabetes
3. Smoking
4. Alcohol use
5. Poor oral hygiene
6. Chemotherapeutic drugs[27]

V.2 Manifestations

The clinical description and history alone will distinguish BRONJ from the following conditions of delayed bone and wound healing.

V.2.1 Clinical Manifestations

Clinical Symptoms and lesions are rather similar to the lesions seen in patients with osteoradionecrosis. Necrotic bone is exposed in the oral cavity. The lesions are often painless; however, the patients may suffer from pain because of surrounding inflammatory soft tissue reactions and show symptoms and radiological signs of bone sequestration and /or osteomyelitis. Tooth extraction is very common in the history of these patients. Interestingly, this disorder seems to be less prominently localized in the mandible in comparison with osteoradionecrosis[28].

V.2.2 Radiographic manifestations

The condition manifests at first panoramic view, with osteolysis or sequestrum in few patients, however with computerized tomography osteosclerosis and/or osteolysis is always found.[29]

Other findings include sclerosis, cortical irregularity, lucency, mottling, fragmentation/sequestra formation, sinus communication, and persistent sockets. There correlation between the anatomic location of clinical and radiographic findings is a high. Treister, Friedland and Woos reported in their study that in nearly all cases, CBCT demonstrated a greater extent and quality of changes compared with panoramic radiography.[30]

V.2.3 Microscopic manifestatitons:

Microscopically, it presents an appearance of nonspecific necrotic bone with some bacterial colonization, similar to that of osteomyelitis or osteoradionecrosis.

Histopathologic examination revealed a necrotic osteitis associated with a mixed infiltrate of lymphocytes and granulocytes with medullary fibrosis and colonization with pathogens[29].

It has been found that Actinomyes is detectable in a high percentage of patients suffering from infected osteoradionecrosis. Interestingly, Lugassy[31] et al. describe two patients with severe osteomyelitis and presence of Actinomyces colonies after bisphosphonate therapy[28].

V.3 Process

The onset of osteonecrosis is related to the potency and half-life of the specific bisphosphonate used. The most potent, Zometa, when administered at the recommended dose of 4mg per month, may produce exposed bone within 6 to 12 months[32].

An equally potent dose of Pamidronate (ie, 90mg per month), administrated on a regular basis, seems to produce exposed bone in 10 to 16 months[24].

On the other hand oral bisphosphonate Fosamax (alendronate), when administered as recommended at 10mg daily or 70mg weekly, takes 3 years or more to produce bone exposure because of its significantly slightly shorter half-life[24].

All patients who received a bisphosphonate absorb a certain amount of bone toxicity. The jaws then undergo bone turnover/renewal at a rate 10 times faster than any other bone in the adult skeleton and are exposed to a tenfold greater effect from these drugs as a result[32].

V.4 American Association of Oral and Maxillofacial Surgeon presented the following bisphosphonate related osteonecrosis of the jaws staging

BRONJ† Staging	Treatment Strategies‡
At risk category No apparent exposed/necrotic bone in patients who have been treated with either oral or IV bisphosphonates	• No treatment indicated • Patient education
Stage 1 Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection	• Antibacterial mouth rinse • Clinical follow-up on a quarterly basis • Patient education and review of indications for continued bisphosphonate therapy
Stage 2 Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	• Symptomatic treatment with broad-spectrum oral antibiotics, e.g. penicillin, cephalexin, clindamycin, or 1st generation fluoroquinolone • Oral antibacterial mouth rinse • Pain control • Only superficial debridements to relieve soft tissue irritation
Stage 3 Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border	• Antibacterial mouth rinse • Antibiotic therapy and pain control • Surgical debridement/resection for longer term palliation of infection and pain

† Necrotic and exposed bone in the maxillofacial region without resolution in 8 to 12 weeks in patients treated with any bisphosphonate and who have not received radiation therapy to the jaws.

‡ Regardless of the disease stage, the following should be done:

Mobile segments of bony sequestrum to be removed without exposing uninvolved bone. Consider to extract a symptomatic teeth within exposed, necrotic bone since it is unlikely that the extraction will exacerbate the established necrotic process.

‡ No short-term benefit, if the IV bisphosphonates is discontinued. However, if systemic conditions allow discontinuing for a long-term, it may be beneficial in stabilizing the sites of BRONJ, and it will reduce the risk of new site development, and will reduce clinical symptoms. The treating oncologist in consultation with the OMS and the patient should discuss the risks and benefits of continuing bisphosphonate therapy.

‡ Gradual improvement in clinical disease has been associated to discontinuation of oral bisphosphonate therapy in patients with BRONJ.

If systemic conditions permit, modification or cessation of oral bisphosphonate therapy should be done in consultation with the treating physician and the patient[27].

VI. MATERIAL AND METHODS

VI.1 Patients:

For Data collection, we required the electronic medical record system used by Zurich University Hospital (KISIM) and by the Department of Oral and Maxillofacial Surgery at the University Dental Clinic (VITODENT). Patients who were treated at the Department for Craniomaxillofacial Surgery, University Hospital of Zurich with BRONJ during 2003 and 2009 were determined.

Our inclusion criteria were that patients have clinical features of Osteonecrosis of the Jaw and who have a bisphosphonate history of at least 3 months, but have no history of radiation in head and neck area.

In total we treated 56 patients with Osteonecrosis of the Jaw and Bisphosphonate history. Of those 56 patients, one had to be excluded due to the fact of radiation therapy in the area of clinical symptoms.

43 (78.18%) of the patients, received chemotherapy, 6 (10.92%) had a history of stem cell transplantation, 10 (18.18%) underwent hormone therapy, 17 (30.91%) received cortisone and 1 (1.82%) received radiotherapy in the oral and neck area.

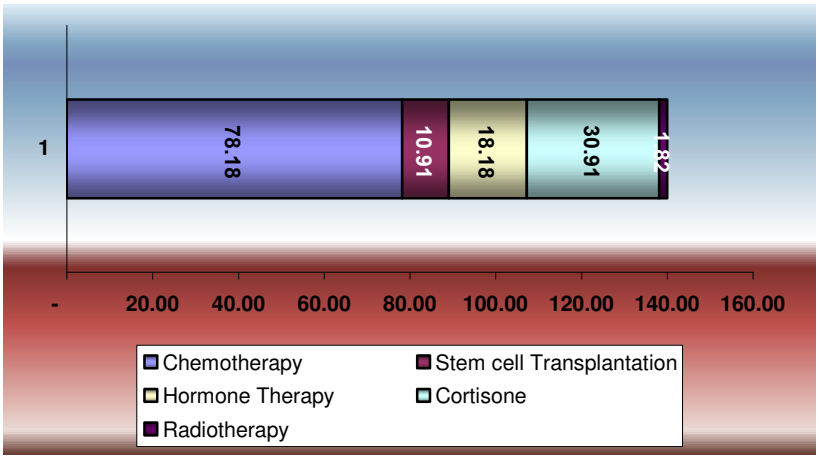

Figure 1: Underlying Cancer Therapy.

VI.2 Methods:

The patients who fulfilled the entry criteria underwent retrospective analysis. Available data on demographics, medical history, type and duration of BP use, possible triggering event, clinical manifestations, mode of therapy and outcome were recorded on different tables on an Excel programm.

The exactly groups were as follow:

1. Patients data: age and sex were recollected
2. Medical History: the underlying these of the patients was taken in consideration. Breast Ca., Multiple Myeloma, Prostate Ca or Osteonecrosis were expected, but any other disease found, was recorded as well.
3. Bisphosphonate History: type of bisphophonate, route of administration (IV or oral), and the duration of the therapy in months was recorded.
4. Clinical Manifestations: Location and distribution of the lesion, first symptomes, and other symptomes during the check ups were recorded
5. Triggering events: last procedure made before finding the first lesion was recorded.
6. Diagnostic Tools: they were made at the first consultation at the Clinic of the University hospital, not on the other clinics. And was only recorded once in this study.
7. Treatment Protocols: antibiocal treatment vs surgical procedures that included minimal invasive curetage as well as ostectomy or extensive resection were recorded.
8. Follow-up and treatment outcome: it was only recorded the information that was found at the moment of the data recollection, which gave us a period of 4 months until 4 years follow up.

VII. RESULTS

VII.1 Patients

The study group included 55 patients, with an average age of 67. Of these patients, 34 were women (mean age, 69 years; range, 47-83 years) and 21 were men (mean age, 63 years; range, 39-82) diagnosed as having Bisphosphonate asociated osteonecrosis of the Jaws.

VII.2 Medical History:

Of all patients, 20 (36.36%) had Breast Cancer, 14 (45.45%) Multiple Myeloma, 6 (10.91%) Prostate Cancer, 8 (14.55%) had a diagnosis of Osteoporosis. And 7 (12.73%) presented other malignancies such as: Bone Cancer, Adenocarcinom, Bladder Cancer, Lung Cancer, No Hodgkin Lymphom and Polyarthritis.

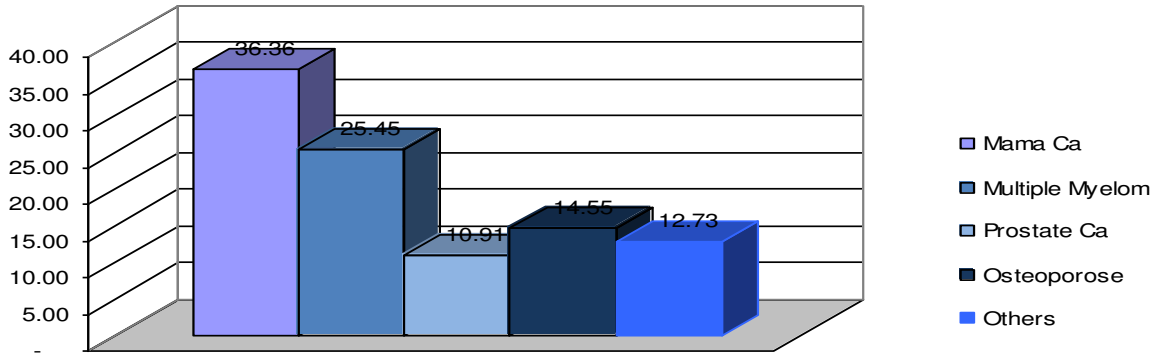

Figure 2: Differentiation of main diagnosis and reason for bisphosphonate therapy.

VII.3 Bisphosphonate History

The patients were mostly receiving their doses intravenously (49; 90.74 %) and only 5 patients were taking oral bisphosphonates (9.26%).

Of all patients, 36 (66.67%) received zolendronic acid 4mg intravenously every 3 to 4 weeks, 6 (11.11%) received pamidronate disodium 90 mg intravenously at the same interval, 7 (12.96%) received both bisphosphonates, beginning with pamidronate and switching to zolendronic acid after a certain period.

Of all patients, 5 (9.26%) were taking oral bisphosphonates, of these patients 3 (80%) were taking Fosamax 70mg once a week and only 1 (20%) was was taking Actonel 30mg once a week.

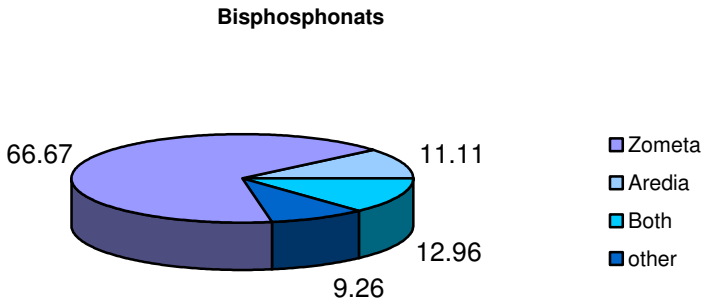

Figure 3: Differentiation of Bisphosphonate intake.

The mean duration from the first use of the drug to the recognition by the patient or physician of sign or symptoms of ONJ was 39 months (range, 3 – 168 months)

The mean duration for each bisphosphonate are to be seen in the following table.

Table 1: Months of Bisphonates intake

	Bisphosphonates intake			
	Zometa	**Aredia**	**Both**	**Other**
Min	6	3	14	18
Max	168	120	60	120
Media	35	44.6	39.12	52.8

VII.4 Clinical Manifestations

The location of the lesion was as follows: 11 (20.4%) patients presented a lesion in the maxilla (3 on the right side and 8 on the left side); 43 (79.6%) patients presented a lesion in the mandibular bone (17 on the right side, 23 on the left side and 3 on both sides).

Table 2: Distribution of Clinical Manifestation

Location				
Maxilla	**Mandible**	**Right**	**Left**	**Both sides**
11	43	20	31	3
20.4	79.6	37.0	57.4	5.6

The first and most frequent first symptom was pain, being the reason for the patient to be evaluated. The patients presented the following first signs and symptoms: Pain on 26 (48.15%), non-healing wounds on 12 (22.22%), swelling on 9 (16.67%), bone exposure on 4 (7.41%) but was seing in more patients in the next controls, and fistulae on 3 (5.56%)

Table 3: Distribution of First Symptomes

1st Symptome				
Non-healing	**Bone exposure**	**Fistula**	**Pain**	**Swelling**
12	4	3	26	9
22.22	7.41	5.56	48.15	16.67

Most of the patients had more than one clinical manifestation of BRONJ. Detailed information was only available for 53 patients (96.36%). Of these patients, 6 (11.11%) presented halitosis, 9 (16.67%) hypesthesia, 25 (46.30%) pus exsudates and 26 (48.15) swelling. 39(72.22%) patients presented non-healing wounds after a procedure and 43 (79.63%) showed exposed bone, which appeared spontaneously or after a procedure.

Other Symptomes					
hypaesth.	swelling	pus	halithosis	non healing	exposed bone
9	26	25	6	39	43
16.67	48.15	46.30	11.11	72.22	79.63

Table 4: Distribution of other Symptomes

The size of the bone exposure was only available on 47 patients, which gave as a media size of 0.88cm

VII.5 Triggering events

Information on local events that triggered the BRONJ was available for 53 patients (96.36%). Before the occurrence of ONJ, 38 patients (71.70%) had a one or more tooth extracted, 1 (1.89%) received an implant and 3 (5.66%) received and implantat after a tooth extraction, 8 patients (15.09%) had other procedures including root canal or periodontal treatments. Lesions developed spontaneously in only 3 patients (5.66%)

Table 5: Triggering procedures

Ex	Implant	both	others	None Tx
38	1	3	8	3
71.70	1.89	5.66	15.09	5.66

VII.6 Diagnostic tools

Different diagnostic tools that were taking in consideration are the ones that were done at the first visit of the patient at the clinic of the university hospital. However, this information was not available for all patients or the procedures were made during the next visits.

The level of leucocytes was only measured in 21 patients (38.4%). The media level was 8.8 10E9/l (range; 2.91 – 18.3 10E9/l). CRP was only measured in 19 patients (35.18%). The media level was 49.52 (range; 3 – 180).

Of the Patients with a CRP value, 7 (36.84%) had a Mama Ca., 4 (21.05%) had Multiple Myeloma and 3 (15.78%) had Protate Ca. And eventhogh they were all receiving IV Bisphosphonates, only 3 patients with Mama Ca and 2 patients with Prostate Ca. had a complete remission of the BONJ.
Histopathology was available for 31 patients (57.4%). Of these patients 16 (51%) presented Actinomyces colonies, 19 (61.29%) presented bone necrosis, 1 (3%) presented partial necrosis and 7 (22.58%) presented osteomyelitis. Microbiology studies were only done in 9 patients (16.67%) and they did not succeed in culturing the Actinomyces or any other specific pathogen.

Image diagnostic test included Orthopanthomgraphy, CT scans and MRIs. It was found that these were done on the first visit on 27 (50%), 29 (53.70%) and 26 (48.15%) respectively. The imaging was part of another study, so the imaging results were not followed in detail.

VII.7 Treatment Protocols

Treatment of the disease was done individually, depending on the severity, size dimension of the jaw necrosis and the underlying disease and general condition of the patient. Surgical treatments were done in 31 patients (57.47%) and no surgical treatments which involved only antibiotics were done in 23 patients (42.59%)

Surgical procedures were considered from small wound curettage up tol an ostectomy of the necrotic bone or extensive resection. Because in some cases more than one surgery was performed, in this thesis, the first action of treatment that was performed is the only one being taken into consideration

In referral to the antibiotics intake, patients received either oral or intravenous amoxicillin (26 patients, 48.15%) depending on the severity of the cases. The patients with allergic reactions to penicillin, clindamicine (24 patients, 44.44%) was prescribed. These drugs were administered for a period of 1 to 16 weeks (media intake, 5.3 weeks)

Antibiotics		
Amoxiciline	**Clindamicine**	**Others**
26	24	7
48.15	44.44	12.96

Table 6: Antibiotics intake

Antibiotics Duration in weeks	
Media	5.3
Max	16
Min	1

Table 7: Time period of Antibiotic intake

VII.8 Follow – up and treatment outcome

Follow – up information was available for 52 patients (96.30%) and ranged between 1 to 208 weeks (4 years). Patient response was classified as follows: CR or complete remission when there was a complete resolution of the BRONJ, PR or partial remission, when there was a reduction of bone exposure, significant pain relief and cessation of pus exudaes and extraoral manifestations, and NR or no response when there was no sign of improvement.

Of the patients, 21 (38.29%) had CR to therapy whereas 22 (40.74) had a PR and 10 (18.52%) had NR. During the study 7 patients (12.96) died because of the main diagnosis not because of BRONJ.

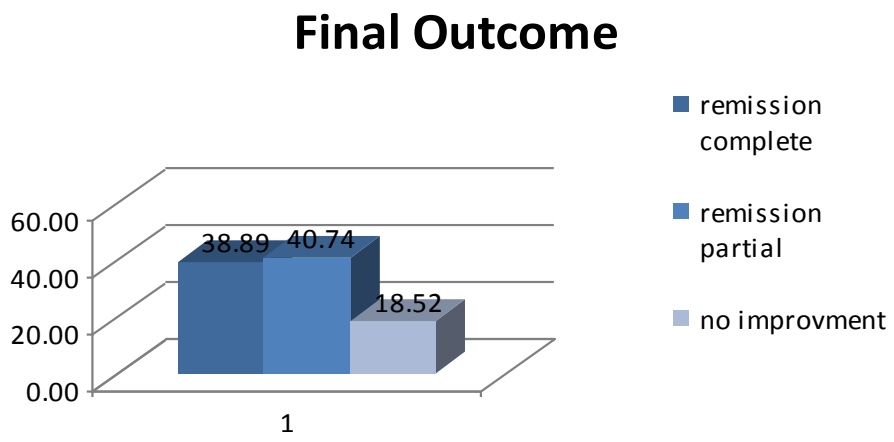

Figure 3

When evaluating which therapy had a better outcome, eventhough the final outcome varied in period of time and how many check ups were done to the patients, no significant difference was found between the CR group with 21 patients and PR group with 22 patients. Of the first group, 13 (61.90%) patients underwent surgery with either local or general anesthesics, and of the second group, 13 (59.09%) underwent therapy under the same conditions. And they also received antibiotics after surgery.

In referal to the Antibiotics intake, only one patient who was receiving Amoxicilin with Clavulanic Acid for more than 12 weeks presented no improvement after this period of time.. Eventually she passed away during the study out of the bone cancer.

VIII. Discussion

Every year, an estimated 30 million bisphosphonate prescriptions are written. It is estimated that pamidronate and zoledronate have been used in over 2.5 million patients worldwide[33].

The use of bisphosphonates in oncology has had a profound beneficial effect on the management of metastatic bone diseases and the prevention of treatment-induced bone loss until 2003, when a considerable side effect in the jaws was described.

Our review shows that the patients presenting osteonecrosis after taking bisphosphonates were patients suffering from Osteoporosis, Breast and Prostate Cancer as well as Multiple Myeloma.

The variable aspects of predisposing systemic and dental comorbidities, triggering events, duration of Bisphosphonate administration, treamtent protocols, and treatment outcomes have been discussed in the literature[7,32,34,37].

Our results are mainly compared with the one by Lazarovici[37] et al in 2009. in which 105 patients with BIONJ underwent follow-up, and data demogarphics, medical background, type and duration of BP use, possible triggering events, mode of therapy, and outcome were recorded. Information very similar to the one that it is being recollected in this paper.

Of our patients, 78.18% had undergone chemotherapy, compared with the 54% of the patients described by Lazarovici et al[37]. The difference is probably due to the fact that 84.2 % of their patients had had Cancer where as 81.82% of our patients had Malignancies.

An important issue discussed in the literature is the mean duration of bisphosphonates consumption before the development of BRONJ. The mean duration was 35 months for Zometa, 44.6 months for Aredia, and 52.8 months for other bisphosphonates (that

included Fosamax, Bonivia and Actomel) among our Patients. In the study of Lazarovici[37], the mean duration was 27 months for Zometa, 48 months for Aredia and 67 months for Fosamax. Marx et al[32] study reported a mean duration of 9.4 month for Zometa, 14.1 months for Aredia and 36 months for Fosamax.

There is a clear sign that Zometa has a greater pontency as the other bisphosphonates, which will produce an effect in a shorter period of time. Eventhough Fosamax results in our study were not taken separately; we can assume that its effect in time will be shown later, as reported by Lazarovici[37] and Marx [7,19].

Seven of our patients received 2 types of bisphosphonates. Most of them received Aredia unteil they were switched to Zometa. This 7(12.96%) of our patients received this combination for a mean of 39.12 months before any sign of osteonecrosis was shown. Lazarovici et al[37] found a mean duration of 52 months before osteonecrosis of the jaw developed. This lenght of time was unexpectedly longer than the mean duration of Aredia and Zometa when administered alone. On the other hand, Marx et al[30] reported a mean of only 12 months when a combined comsuption of both bisphosphonates was used. Our results show not such a big discrepancy between the intake of each bisphosphonate alone nor when taking together.

Of our patients, 79.6% had the osteonecrosis developed in the mandible, 20.4% had lesions in the maxilla and no lesion was found in the palate. Lazarovici et al[36] reported that 54% of their patients had lesions in the mandible, 34% of their patients had lesions in the maxilla, 11% in both jaws and 1% in the palate.
In reference to the clinical manifestations, Lazarovici et al[37] found that 55.4% of their patients initially presented with exposed bone, 67.32 with pus exudates and 73.26% with complaints of a painful sensation in the affected area, whereas 16.83 exhibited extraoral manifestations, such as swelling and fistulas, mostly in the submandibular area. When mesuring the first signs and symptoms, we found that 48.15% of the patients presented with pain, 22.22% of the patients with non-healing wounds, 16.67% of the patients with swelling, 7.41 % with bone exposure and 5.56% of the patients with fistulae.

Pain is clearly the most common symptom. However this information does not exclude the posibility that a patient could have had another manifestation at first and was not able to notice it.

Information about other clinical manifestations was gathered through out the process, which was only available for 53 patients. From these, it was found that 79.63% of these patients showed exposed bone, which appeared spontaneously or after a procedure; 46.30% had pus exudates, 48.15% had swelling, 11.11% presented halitosis, 16.67% hypesthesia, and 72.22% presented non-healing wounds after a procedure.

Another important issue to discuss is the event that triggers the oral system to develop osteonecrosis. Eventhough there are many scientific studies proving the valuable use of bisphosphonates as a part of the oncology therapy, there is considerable evidence that long term bisphosphonate therapy can induce osteonecrosis, and that this necrotic processes are mostly initiated by local traumas or dental procedures[38].

Dentoalveolar surgery, such as tooth extraction or placement of a dental implant, has been sugested as a predisposing factor for the development of osteonecrosis of the jaws[27,32]. In our study, 50 patients (94.34%) exhibited ONJ after a dentoalveolar surgical procedure, of these patients 71.70% had a tooth or more extracted as a triggering event. Lazarovici et al show that 47 patients (50%) had also undergone a dentoalveolar surgical procedure and that as well here the tooth extraction was the most prevalent event (37 patients). ONJ lesions emerged spontaneously in 3 (5.6%) of our patients, the figure was 40 (43%) in the study of Lazarovici[37].

When evaluating the patients we gathered information regarding their levels of leucocytes and CRP. Unfortunately, this information was not available in all patients and was not taken necesarely on the date of admission. In order to find a relevant information regarding this topic, further studies should be done.

Actinomyces has been found to be detectable in a high percentage of patients suffering from infected osteonecrosis. Interestingly, Lugassy[31] et al. described two patients with

severe osteomyelitis and presence of Actinomyces colonies after bisphosphonate therapy. Recently, Melo and Obeid[35,38] reported on a similar case with Actinomyces osteomyelitis in a patient treated with zolendronate because of metastatic breast cancer. Lazarovici et al[35] identified actinomyces in the histopahtologic examinations of 93% their cases. We found that out of the 31 patients, who had a histopathologic examination, 51% contained actinomyces colonies. The actual role of this pathogen in the pathogenesis of osteonecrosis is still not clear.

Because our study recollected data since 2003, when the first case of bisphosphonate induced osteonecrosis of the jaw was reported, there was not specific protocol of treatment. We found that during the first years, minivmal invasive surgery with a conservative paleative use of antibiotics was the first option and within the time surgery has become the first choice.

However, as mention before, it is only taken in consideration the first action of treatment that was performed, which resulted in 57.47% of our patients getting surgical treatments. No surgical treatments which involved only antibiotics were applied in 42.59% of the patients. Lazarovici et al[36] developed a departmental treatment protocol, whose main goal was to provide a conservative paleative treatment. However surgery was performed on 24.75% of their patients.

In Taiwan, Dr. Chiu[39] and team studied 12 patients with diagnosed BRONJ. Modified therapeutic strategies for these patients were graded according to the severity of BRONJ. In the modified stage 2 patients (25%), antibiotic therapy of minor debridement surgery was useful for obtaining complete remission in all symptomatic patients. All modified stage 3 patients (75%) received antibiotic therapy, sequestrectomy, and debridement of necrotic bone.

Antibiotics intake was administered to all of our patients, either with or without a previous surgery. Our patients received either oral or intravenous amoxicillin (48.15%) depending on the severity of the cases. Patients with allergic reactions to penicillin, recivied clindamicine (44.44%) instead. Lazarovici et al[37] administered oral amoxicillin to 50.49%

of their patients, IV penicillin to 8.91%, oral doxycycline to 27.725 of their patients, oral clindamycin to 9.9% of their patients and IV clindamycin to 1.98% of their patients. The antibiotics of choise remained the same in both studies.
Lazarovici et al‘s conservative protocol together with an empiric antibiotic treatment led to the following results amor theri study patients: 16 (18%) had a CR, 45 (52%) had a PR, and only 26 (30%) had NR. These findings are similar to ours, which showed that 21 (38.29%) had CR, 22 (40.74%) had a PR and 10 (18.52%) had NR.

General data on treatment outcome of osteonecrosis of the jaw in the literature remains vague, and need to be evaluated.

IX. Conclusion

Induced osteonecrosis of the jaws is one of the most studied pathology in these days. And eventhough there is considerable evidence that the use of bisphosphonates either orally or intravenously can induce jaw osteonecrosis, there is still a lot of information unknown.

There is a broad agreement among reserarchers that the standard goal for controlling this type of osteonecrosis is to prevent it. However, in order to be able to prevent it, it is necessary to to know how it works since the very first start.

After all these evidence, many believe that BRONJ is definitively caused by bisphosphonates. However, how sure we are about this. Are they really the cause? It is said that their point of action is to affect the bone turnover specially affecting the osteoclast function. But during the process of healing we can observe many different points that can be affected and that may lead us to think that bisphosphonate are acting in different levels.

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